Request for Application for Data Management and Coordinating Center

This is the Request for Application (RFA) for the EDRN Data Management and Coordinating Center.

THE EARLY DETECTION RESEARCH NETWORK: DATA MANAGEMENT AND COORDINATING CENTER

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P.T.

National Cancer Institute

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PURPOSE

The Division of Cancer Prevention (DCP), National Cancer Institute (NCI), invites applications for cooperative agreements to establish a national Network that will have responsibility for the development, evaluation, and validation of biomarkers for earlier cancer detection and risk assessment. Biomarkers are defined as cellular, biochemical, molecular, or genetic alterations by which a normal or abnormal biologic process can be recognized or monitored. Biomarkers are measurable in biological media, such as in tissues, cells, or fluids. The purpose of the Network is to establish a scientific consortium of investigators, academic as well as industrial, with resources for basic, translational, and clinical research. The consortium will have three main components -- Biomarkers Developmental Laboratories, Biomarkers Validation Laboratories, and Clinical/Epidemiologic Centers. The Biomarkers Developmental Laboratories will have responsibility for the development and characterization of new or refinement of existing biomarkers; the Biomarkers Validation Laboratories will serve as a Network resource for clinical and laboratory validation of biomarkers, which include technological development and refinement; and the Clinical/Epidemiology Centers will conduct clinical and epidemiological research regarding the clinical application of biomarkers. A Steering Committee composed of the Principal Investigators in the Network and appropriate NCI staff will coordinate the work of the consortium. Logistic support and informatics will be provided through an auxiliary Data Management and Coordinating Center.

The purpose of this Request for Applications (RFA) is to establish the Data Management and Coordinating Center. RFAs were previously issued for:

Biomarkers Developmental Laboratories - CA-98-028
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-98-028.html

Biomarkers Clinical/Epidemiologic Centers - CA-99-007
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-007.html

Biomarkers Validation Laboratories - CA-99-008
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-008.html

Applicants are encouraged to seek funding to participate in more than one component.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national

activity for setting priority areas. This RFA, Early Detection Research Network: Data Management and Coordinating Center, is related to the priority area of cancer prevention. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800), or at http://www.crisny.org/health/us/health7.html.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and Local governments, and eligible agencies of the Federal Government. Domestic institutions may propose collaborations/ consortia with foreign institutions. Applications will not be accepted from foreign institutions.

An applicant may be an academic institution; a clinic; or a combination of academic institutions, hospitals, clinics, clinical trial cooperative groups, and/or health maintenance organizations that agree to work together with a principal investigator and a single administrative focus.

MECHANISM OF SUPPORT

The administrative and funding instrument to be used for this program will be a cooperative agreement (U01), an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Details of the responsibilities, relationships and governance of the study to be funded under cooperative agreement(s) are discussed later in this document under the section "Terms and Conditions of Award."

The total project period for applications submitted in response to this RFA may not exceed five years. The anticipated award date is April 2000.

Awards and level of support depend on receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of the NCI, awards pursuant to this RFA are contingent upon the availability of funds for this purpose.

At this time the NCI anticipates that there will be a renewed competition after five years. If the NCI does not continue the program, awardees may submit grant applications through the usual investigator-initiated grants program. However, before submitting such an application, applicants are advised to contact the program director listed under the INQUIRIES section.

FUNDS AVAILABLE

An estimated $400,000 will be available per year for the first project period. Only one award will be made. Funding beyond the initial budget period will be contingent on the continued availability of funds for this purpose, and the continued progress of the awardees and the Network as a whole. At the present time, the NCI has not determined whether or how this solicitation will be continued beyond the present RFA and related RFAs for the Network.

RESEARCH OBJECTIVES

Background

Although the primary tumor can usually be controlled by local therapy, most

cancer deaths are caused by metastatic disease. The goal of early detection and screening is therefore the diagnosis and treatment of cancer before it spreads beyond the organ of origin, perhaps even in its pre-invasive state. Unfortunately, available early detection and screening techniques pick up many tumors at a relatively late stage in their natural history. As a result, decrements in mortality with the current available detection modalities are likely to be modest. New technologies coming from the field of molecular and cellular biology are able to identify genetic as well as antigenic changes during the early stages of malignant progression. Some of these changes show promise as biomarkers for preneoplastic development or for early malignant transformation. The application of these emerging technologies in the field of early detection and risk assessment is a high priority in the National Cancer Institute's strategy for reducing mortality from cancer. Detection of early cancer has been identified as an area of extraordinary opportunity for investment in the NCI 2000 Bypass Budget.

Data show that detection and prompt treatment of pre-malignant or small lesions can reduce mortality, for instance, from mammography and Pap screening. Therefore, it seems reasonable to explore the application of the new molecular-based technologies for earlier and more specific detection and even for risk assessment, that is, before the cancer physically develops in order to institute chemoprevention. These are the overarching goals of the research Network.

The continued acceleration of scientific progress is no doubt faster than it has ever been; consequently, the need for clinical application is now greater than ever. Research in molecular genetics, cell biology, protein chemistry and immunology has found that cells undergo many changes during neoplastic progression. Often occurring early in the malignant process, these changes include, for example, production of novel proteins, growth factors, cytokines, etc., in addition to multiple genetic alterations. Because these changes have been associated with malignant transformation, they are now recognized as biomarkers for cancer. Such biomarkers, whether present in tissue, serum, urine, etc., could serve as indicators of early cancer or as markers of risk for impending cancer.

Early detection technologies are also rapidly evolving while existing technologies are undergoing progressive refinement in their sensitivity, specificity, and throughput. Improved analytic tools have allowed a more detailed examination of the molecular basis of carcinogenesis and provided the ability to identify the molecular and cellular signatures of cancer and to explore gene-environment interactions relevant to early detection. To explore fully the application of molecular profiles for earlier detection and risk assessment, it is essential to understand the molecular pathogenesis of cancer, that is, the natural history of tumor progression at the molecular level, so that the biological behavior of an evolving lesion (for example, dysplasia or field change) can be predicted with greater accuracy. Current observations indicate that cancers usually evolve through many complex cellular processes, pathways, and networks. A better understanding of the circuits in these pathways is critical if we are to successfully apply these molecular-based technologies to earlier detection.

Progress in the field, however, is currently impeded by some practical hurdles. The systematic application of biomarkers for earlier cancer detection or even for risk assessment has been fragmented and not well coordinated. While studies conducted by individual investigators have been useful in advancing our understanding of carcinogenesis, there has been a lack of research emphasis on the continuum from preclinical tumor development to early evaluation of new techniques and their clinical application. In many of these reported studies the investigators have not been able to explore fully the biological implications or to test systematically the clinical application of these molecular markers. This has resulted, in part, from the lack of a stable connection between basic laboratory research and the opportunity for rapid clinical evaluation. Other factors contributing to the lack of systematic

evaluation include the non-availability of high quality matched specimens from normal, suspicious, preneoplastic and multistage neoplastic lesions along with demographic and follow-up data. As a consequence, much work in this area has been fragmented into numerous small and disconnected studies without complete evaluation. Usually, the results of these studies cannot be generalized to the population as a whole.

Objectives (applicable to Network as a Whole)

This initiative will support the creation of a national Network for early cancer detection with resources for translational research that will include the laboratory sciences, clinical sciences, public health, biostatistics, informatics, and computer sciences. The goals of the Network will be to discover and to coordinate the evaluation of biomarkers/reagents for the earlier detection of cancer and for the assessment of risk. Specifically, the objectives of the Network will include:

-- the development and testing of promising biomarkers or technologies in institutions having the scientific and clinical expertise, in order to obtain preliminary information that will guide further testing;

-- the timely and early phase evaluation of promising, analytically proven biomarkers or technologies. Evaluation will include measures of diagnostic predictive accuracy, sensitivity, specificity, and whenever possible, medical benefits, such as predictors of clinical outcome or as surrogate endpoints for early detection and for prevention intervention clinical trials;

-- the timely development of biomarkers and expression patterns, sometimes of multiple markers simultaneously, which will serve as background information for subsequent large definitive validation studies in the field of cancer detection and screening;

-- collaboration among academic and industrial leaders in molecular biology, molecular genetics, clinical oncology, computer science, public health, etc., for the development of high throughput, sensitive assay methods for biomarkers from an early detection and risk assessment viewpoint;

-- conducting early phases of clinical/epidemiological studies, e.g. cross-sectional, retrospective, to evaluate predictive value of biomarkers; and

-- encourage collaboration and rapid dissemination of information among awardees to ensure progress and avoid fragmentation of effort.

The ultimate impact of the new technology on reducing mortality will not be felt until highly predictive biomarkers are developed for earlier cancer detection or for risk assessment. The success of this effort depends in large measure on exploring the concordance between genetic or molecular markers and the morphologic changes associated with premalignant and pre-invasive lesions that have life-threatening potential. In other words, we need to identify biomarkers that are predictive of clinical outcomes.

Because early detection and treatment issues are often related, the Network will need meaningful participation from various medical organizations. In some of its activities, the Network may need to relate programmatically to the research infrastructures supported by NCI (for example, the Specialized Programs of Research Excellence, Cancer Genetics Network, Breast and Colon Cancer Family Registries, Cooperative Human Tissue Network, Cancer Genome Anatomy Project), with ongoing NCI clinical research programs/trials (for example, the Clinical Community Oncology Program); or with other health agencies, such as the Food and Drug Administration, Department of Defense, and Veterans Administration. Certain types of trials in earlier detection, especially those involving interventions, may best be conducted as intergroup studies with treatment-oriented cooperative groups, such as the NCI Clinical Cooperative Groups, NCI designated Cancer Centers, international

collaborators, and health maintenance organizations. The need for such cooperation should be anticipated and provided by the Network leadership.

Scope (applies to this RFA)

The scope of this RFA is to establish the Data Management and Coordinating Center to coordinate the activities of the Network and to provide logistic support for the conduct of the Steering Committee meetings, provide statistical and data management support for protocol development, conduct analysis and develop relevant informatics. The Data Management and Coordinating Center will also conduct studies in applied and theoretical approaches that relate specific patterns of array analyses to risk assessment and disease prediction. Specifically, the DMCC will be responsible for three major Network activities: (1). Network Coordination, (2). Data Management, and (3). Theoretical and Applied Research. Before submission, it is recommended that applicants consult companion RFAs: CA-98-028 (The Early Detection Research Network: Biomarker Developmental Laboratories, NIH Guide, January 20, 1999), CA-99-008 (The Early Detection Research Network: Biomarker Validation Laboratories, NIH Guide, March 5, 1999).

1. Network Coordination: It is expected that the DMCC will:

- provide logistical and administrative assistance in arranging meetings of the Steering Committee and the Advisory Committee, arranging Workshops, and providing other operational support for the Network (e.g., communications, subcommittee meetings). The DMCC will prepare, distribute, and maintain minutes of the meetings.
- produce and maintain all documents, including Network Operating Policy and Procedures manuals.
- support the development, coordination, and implementation of collaborative research protocols within the Network infrastructure.
- assist in the collection of epidemiologic information, data analysis, study designs quality assurance for a central database, statistical analyses of pooled data, and distribution of specimens stored at sites participating in the Network.
- develop and maintain an interactive Web page to publicize EDRN, announce the availability of EDRN-supported resources and receive input from investigators.
- develop and maintain a "listserv" interactive email system for communication within the Network.

2. Data Management: The DMCC under the direction of the Steering Committee will:

- develop and maintain computerized data system for data management and statistical analysis.This may not be very intensive in the initial two years.
- develop worksheets and study data as needed for the collection of data in multi-center biomarkers validation studies, verify all data, develop test, and maintain software for within-form edit checks at data entry.
- develop uniform investigative protocols for data and specimen collection.
- ensure that data are collected to determine the benefits and risks that follow from positive or negative test results.
- provide support services for the production of data forms and reports, graphics, and other materials as required.
- provide a mechanism for rapid and routine (to be decided by the Steering Committee) transmittal of materials (e.g. computer output, reports, etc.) among the network participants and the NCI Program Director.
- monitor Network protocol adherence, data collection and data submission, and report violations to the Steering Committee.

3. Theoretical and Applied Research: It is expected that DMCC will assist the Steering Committee and conduct research on the development of statistical and computational tools, some examples of which, are provided below:

- With the rapid development of array technology for DNA, RNA, and protein based markers, it is possible to detect multiple genomic abnormalities simultaneously. Due to the complex interactions among these markers, the DMCC will explore statistical/computer methods that predict whether a specific pattern will indicate that an individual is at higher risk than the population for developing cancer.
- develop analytical tools for analyzing expression data (from DNA, RNA, or protein array expression) with respect to clinical endpoints.
- development of new analytical software to extract novel, relevant information on potential biomarkers from the genomic databases, such as Cancer Genome Anatomy Project (CGAP).

Capability and Characteristics of the Data Management and Coordinating Center: The expertise of the Data Management and Coordinating Center should include logistic support capability plus expertise in biostatistics and information technology. As the Network gains experience and its responsibilities shift and broaden, the number and identity of the personnel should change in response to the scientific opportunities. Qualified investigators in the Data Management and Coordinating Center should be invited to assume responsibility in a flexible manner as the need arises.

Scientific Agenda: Applicants of the Data Management and Coordinating Center should develop and articulate a plan that summarizes their views and their anticipated lines of research for the issues discussed above on which they choose to focus.

NETWORK ORGANIZATION

Network Components

The Early Detection Research Network will consist of four components: 1) the Consortium, 2) a Steering Committee (SC), 3) an Advisory Committee (AC), and 4) a Data Management and Coordinating Center.

Consortium: The Consortium will consist of three scientific components: i) the Biomarkers Developmental Laboratories (BDL), ii) the Biomarkers Validation Laboratories (BVL), and iii) the Clinical/Epidemiologic Centers (CEC). These three components jointly will be known as the Consortium for Biomarkers in Early Detection Research (CBEDR) and will be assembled by the NCI. Each component will be funded through a separate Request-for-Application. An applicant, however, may seek funding to participate in more than one component. The awardee will conduct independent research using the U01 or U24 funds and collaborative research using the Core Funds from the Headquarters (see definition of "Headquarters" below) and from the set-aside funds in the U01 or U24 awards pending approval by the Steering Committee and release by the NCI, respectively.

Each laboratory/center, which will be managed by a Principal Investigator, may include academic and industrial biotechnology investigators who are involved in cancer detection and diagnostic research. In order to expedite the translational research, the Consortium may be supplemented by the ad hoc participation of additional investigators (academic, industrial or community-based) who are able to complement or conduct studies within the Network.

It is anticipated that the CBEDR will consist of experts in molecular biology, laboratory technology, clinical studies, biometry, and in epidemiology. The expertise in laboratory science should include research in the biology of incipient neoplasia as well as the development, characterization, and testing of biomarkers of early cancer and risk, development of relevant technologies for biomarker detection, and analytical tools for the evaluation of biomarkers for detection and risk assessment. The expertise in laboratory validation should include knowledge and practice of Standard Operating Procedures (SOPs), and experience in the statistical evaluation of accuracy (both for clinical and experimental tests), precision, reproducibility, and performance

characteristics of tests in multi-institutional settings. Expertise in patient accrual and associated clinical issues for pilot studies will be needed to apply basic science discoveries to clinical settings. Computational and informatic needs of the Consortium will be provided by a Data Management and Coordinating Center. Therefore, the Consortium, in concert with the Steering Committee, the Advisory Committee, and the Data Management and Coordinating Center will constitute the Network (see definition of "Network" above). An NIH intramural laboratory may be one of the research members in the Biomarkers Developmental Laboratories within the Consortium.

Steering Committee: The Steering Committee will have major scientific management oversight, including monitoring the activities of the Data Management and Coordinating Center. For administrative structure, and responsibilities of the Steering Committee, see "Collaborative Responsibilities."

Advisory Committee: An independent Advisory Committee will be established by the NCI to ensure that the overall Network is adequately responsive to promising opportunities, exhibits the desired degree of flexibility in composition and decision-making and makes prioritization decisions free from conflicts of interest. For further details, see "Collaborative Responsibilities."

Data Management and Coordinating Center: The Data Management and Coordinating Center will provide logistic support for the conduct of the Steering and Advisory Committee meetings, provide statistical and data management support for Network collaborative studies, including protocol development, analysis of clinical data, and informatics. It will study applied and theoretical approaches to the simultaneous analysis of multiple markers. In addition, the Data Management and Coordinating Center will develop common informatic and analytical tools for the interpretation of data and instruments for checking uniformity, consistency, accuracy, timing, reproducibility, and privacy of the data.

Headquarters: The institution of the Chair of the Steering Committee will serve as the Headquarters of the Network. The Chair of the Steering Committee can be any Principal Investigator involved in the Network. The Chair serves as the Principal Investigator of the Headquarter's awards and implements the scientific, operational and organizational policies of the Network. The headquarters provides the executive leadership, scientific direction, and management for the Network. It serves as a center for information dissemination to investigators and institutions in the Network as well as to others outside the Network.

Funds

Funds will reside with 1) the individual awardees in the Consortium For Biomarkers in Early Detection Research, 2) the Data Management and Coordinating Center, and 3) the Headquarters.

Consortium for Biomarkers in Early Detection Research: The Principal Investigators will have funds available through their individual U01 or U24 awards to support the development of the scientific program and clinical protocols. All investigators will be encouraged to seek supplemental funding through the Small Business Innovation Research Award (SBIR, R43 and/or R44), Small Business Technology Transfer (STTR, R41 and/or R42), Exploratory/Developmental grants (R21/R33), and other research support mechanisms.

Data Management and Coordinating Center: The Data Management and Coordinating Center will be funded through a separate RFA.

Core Funds for the Headquarters: Core funds will be available to the Chair of the Steering Committee. Applicants under this RFA need not apply for the Core

Funds in their U01 applications. Core funds are reserved for post-award collaborative Network research and for a variety of other functions, for example:

1. Core funds would be used to expand participation within the Consortium through supplemental funding to an investigator, not part of the Consortium. However, receipt of these supplemental funds does not, in and of itself imply membership on the Steering Committee. Core Funds that are provided for these supplements will represent direct cost only. Facilities and administrative costs will not be provided for research activities supported by the supplemental core funds.

2. Funds will often be needed in moving a new marker test to the point at which it can be validated at multiple centers and in larger populations. Test reagents will require scale-up at this point, and the Steering Committee will require sufficient funding to contract to laboratories or companies that can scale up production and maintain quality of the reagents (e.g.- monoclonal antibodies, labels, etc.) and to Clinical/Epidemiologic Centers for subject accrual. Funds will also be required for data management, travel, meetings, and other collaborative activities of the Network.

The above activities will be supported by the funds that will be added to the Chair's award (The Core Funds). The use of this fund will require NCI approval.

Governance

The Steering Committee will be responsible for coordinating the research effort across the Consortium, including the Data Management and Coordinating Center, and will formulate policies and procedures for the operation and management of the Network.

The following example illustrates the functions of the Network and the support it offers for moving basic research findings into clinical practice.

An investigator within the Consortium identifies a putative biomarker through original laboratory research. Based on the pilot research findings, the putative marker seems to be useful for early cancer detection. The investigator can then approach the Steering Committee for additional evaluation of the marker and possible support for further testing. The Steering Committee then has the responsibility to review the data on the potential marker using its standing formal criteria as a guide. The Steering Committee can consult the Advisory Committee to obtain information on the requirements and need for additional research on the marker. It also can consult the Biomarkers Validation Laboratories and the Clinical Centers regarding requirements for laboratory tests, needs for quality assurance, and the availability of patient groups for clinical validation. If necessary, scientific resources from other Centers can be pooled to conduct studies. Concurrently, the informatics team in the Data Management and Coordinating Center can develop tools for the analysis of results.

There will also be flexibility so that investigators outside the Consortium will be able to collaborate with an existing center or bring their discoveries directly to the Steering Committee (for example, by Letter of Intent). To support such efforts, the Steering Committee will be able to use core funds to supplement the investigator's ongoing research. The investigator, in turn, will agree to share his research findings and become an associate member of the Consortium.

SPECIAL REQUIREMENTS

Definitions

Awardee: The institution to which a cooperative agreement (U01) is awarded.

Principal Investigator (PI): The investigator who is designated by the applicant organization to direct the project that is supported by the U01 grant in response to this RFA. The PI will assume the responsibility and accountability to the applicant organization officials and to the NCI for the performance and the proper conduct of the research supported by the U01 mechanism in accordance with the terms and conditions that are stated in this RFA. The PI will be a voting member of the Steering Committee.

NCI Program Director: A scientist administrator from the NCI extramural staff, the Program Director will not only provide normal stewardship for the U01 grants awarded under this RFA, but will also be substantially involved in the service responsibility and scientific coordination within the Network, will have responsibilities in broad scientific and programmatic issues, and serve as a voting member of the Steering Committee, as defined under the "Terms and Conditions of Award."

Terms and Conditions of Award

These special Terms of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Parts 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements. [Part 92 applies when state and local governments are eligible to apply as a "domestic organization."].

In addition, the following terms and conditions will be incorporated into the U01 award statement, and will be provided to the PI and the awardee institutional official at the time of award.

Under the cooperative agreement, the NCI purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and the NCI Program Director.

A. Rights and Responsibilities of the Data Management and Coordinating Center:

-- The PI of the DMCC will have the primary authority and responsibility to define objectives and approaches, including the logistic support for the Steering Committee, organization of Workshops, and providing assistance for other activities of the Network. The PI will also have responsibility for data management, analysis, and statistical research.

-- The PI of the DMCC will be responsible for accepting and implementing the goals, priorities, common protocols, procedures, and policies agreed upon by the Steering Committee.

-- The PI of the DMCC will assume responsibility for individual protocols/research and collaborative Network projects approved by the Steering Committee.

-- The PI of the DMCC will assume responsibility and accountability to the applicant organization officials and to the NCI for the performance and proper conduct of the research supported by the U01 in accordance with the terms and conditions of the award.

-- The PI of the DMCC will serve as a voting member of the steering committee, will attend the Planning meeting and two Steering Committee meetings in the first year and two Steering Committee meetings a year in subsequent years.

-- The Awardees will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies.

-- The PI of the DMCC will be responsible for collaborating on common research designs or protocols, including methods and requirements for joint participation and collaboration as directed by the Steering Committee, and handling of data, including appropriate sharing of methods and data among collaborating organizations.

B. NCI Extramural Staff Responsibilities

There will be one primary NCI Program Director for the Network. However, the Program Director may be assisted by other NCI staff on specific scientific or programmatic issues as needed.

The NCI Program Director will have substantial scientific programmatic involvement during conduct of this activity, through technical assistance, advice and coordination above and beyond normal program stewardship for grants as described below.

Because of the Network's diverse scientific agenda and the number of tasks that have to be accomplished to achieve its goals, a number of NCI staff members may interact with the Network as needed. The NCI Program Director (a staff member in the Division of Cancer Prevention) will assist the Network on scientific and programmatic issues and advise the Network on the availability of other resources. Staff members from the Chemopreventive Agent Development Branch, NCI, will be available to report the status of intermediate endpoints and on active chemoprevention trials relevant to the Network studies. Staff members from the Biometry Branch, NCI, will also be available to assist the Network on the issues of study design, sample size, and other statistical computations. Other NCI staff may assist and advise the Network on relevant programmatic and scientific issues through the NCI Program Director.

The NCI Program Director will convene the initial meeting of the Steering Committee, have voting membership on the Steering Committee, and, as determined by the Committee, its subcommittees.

Although the PI will have lead responsibilities in all collaborative tasks and research activities, it is anticipated that the NCI Program Director will have lead responsibilities in sharing the broad programmatic issues among awardees.

The NCI reserves the right to adjust funding, withhold support, suspend, terminate, or curtail the study or an individual award in the event of a failure to comply with the Terms and Conditions of Award, substantial shortfall in participant recruitment, follow-up, data reporting, quality control, or other major breach of the protocol, or human subject ethical issues, whenever applicable.

C: Collaborative Responsibilities

Steering Committee: The Steering Committee will have major scientific management oversight and responsibility for developing collaborative Network research designs, protocols and manuals, facilitating the conduct and monitoring of studies, and reporting study results. The Steering Committee will be composed of the Principal Investigators from each member of the Consortium, the Principal Investigator of the Data Management and Coordinating Center, and the NCI Program Director. Each member will have one vote. The Chair (non-NIH person) will be selected by the Steering Committee. The institution of the Chair of the Steering Committee will serve as the Headquarters (for definition, see "Network Organization"). Subcommittees will be established by the Steering Committee, as it deems appropriate; the NCI Program Director will serve on subcommittees as appropriate.

- After all the Network components have been funded, the Steering Committee will convene its first Planning Meeting. Initial responsibilities of the Steering Committee will be to:

1. establish policies and procedures for the operation of the Network;

2. establish policies and procedures for protocols, relations with industry, and collaborative Network-defined projects;

3. establish policies and procedures for reviewing changes in projects not showing translational significance at the request of the laboratories/centers, and making recommendations to the NCI for replacing the project with more promising ones with revised scope and adjusted budget (increase in the budget will not be permitted);

4. set initial standards or "decision criteria" for prioritizing and for validating biomarkers/reagents for further clinical studies;

5. establish policies and procedures for accepting, reviewing, and recommending proposals from investigators outside the Network for supplemental funding and expanding the Network participation;

- The Steering Committee will establish and support a Data and Safety Monitoring Committee for Network collaborative clinical studies to ensure protection of human subjects. The Data and Safety Monitoring Committee should be independent of study leadership and free from conflicts of interest. The Committee will insure that the subjects in clinical studies are protected and that their interests are not made secondary to the interests of the scientific investigation.

- The Steering Committee will review patient accrual, follow-up, protocol compliance, results of audits, and regulatory requirements at the participating Centers and formally report the results of its reviews to the NCI.

- The Steering Committee will promote and foster the inclusion of women and ethnic minorities in clinical studies and assure the completeness of informed consent.

- The Committee will track the collaborative Network research progress and assure that the results of laboratory research and clinical studies are published in peer-reviewed journals in a timely manner and in accordance with the publication policies of the Network.

- At any time during the Network project, the Steering Committee may examine the validation data for biomarkers/reagents developed by the Network, and decide when a biomarker is sufficiently validated, or recommend when to stop non-productive experiments relating to biomarkers validation.

- The Steering Committee will discuss collaborative projects to be pursued jointly with the funds available from Headquarters and from individual U01 or U01 awardees or NIH intramural project budgets.

- The collaborative Network studies/protocols will be approved by the Steering Committee. Data will be submitted centrally to the Data Management and Coordinating Center. The Steering Committee will define the rules regarding access to data and publications.

- The Steering Committee will plan one of several Workshops during the network project period to inform the scientific community and relevant advocacy groups of the progress made toward development and clinical application of biomarkers developed through the Network. The NCI Program Director, the Network Advisory Committee, and other NCI staff will advise the Steering Committee regarding participants for the workshops and symposia. The

Data Management and Coordinating Center will manage the logistics for these meetings.

Advisory Committee:

1. The Advisory Committee will advise the Steering Committee through the NCI on relevant scientific issues, including study design, prioritization of biomarker development, development of collaborative study protocols, including decision criteria for clinical applications, for example, early detection, prognosis, intermediate end point, etc.

2. Membership on the Committee and duration of service will be decided by the NCI in consultation with the Steering Committee. The membership will include members or institutions not participating in the Network. The Advisory Committee will include basic scientists, clinicians, public health scientists, epidemiologists, ethicists, statisticians, and members from relevant advocacy groups. Scientific experts will be drawn from various disciplines relevant to multi-center detection research and experts in data management, biostatistics, and clinical study design.

3. The Chair of the Advisory Committee will be elected by its members. The Chair of the Steering Committee will also serve as a member of the Advisory Committee. The NCI will be represented by program staff. The Chair of the Advisory Committee will also serve as a member of the Steering Committee.

4. The Advisory Committee will evaluate the progress and success of the Network against the criteria developed by the Steering Committee.

5. The Advisory Committee will assist the NCI on site visits to the participating institutions, as necessary.

6. The Advisory Committee will collaborate with the Steering Committee to suggest participants for and to assist in the implementation of workshops and symposia and to provide liaison between the cancer research community and the Network.

Data Safety and Monitoring Committee:

The Data Safety and Monitoring Committee will be appointed by and report to the Steering Committee in consultation with the NCI Program Director who will also be the member of this committee. The Data Safety and Monitoring Committee will be composed of external, non-participating scientists appointed by the Steering Committee to monitor patient safety, conduct data audits, and document progress to the NCI Program Director and the Advisory Committee.

D. Arbitration

A panel will be formed to review any scientific or programmatic disagreement (within the scope of the U01 award) between U01 awardees and the NCI. The panel will be composed of three members: one selected by the Steering Committee (with the NCI Program Director not voting), or by an individual U01 awardee in the event of an individual disagreement; a second member selected by the NCI; and, the third member selected by the two prior selected members. Any disagreement that may arise on scientific/programmatic matters (within the scope of the award), between award recipients and the NCI may be brought to arbitration.

This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993.

All investigators proposing research involving human subjects should consult the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994.

Investigators may also obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are clear and compelling scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should consult the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

LETTER OF INTENT

Prospective applicants are asked to submit, by June 11, 1999 a letter of intent that includes a descriptive title of the proposed research, name, address, and telephone number of the Principal Investigator, identities of other key personnel and participating institutions, and number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information allows NCI staff to estimate the potential review workload and to avoid conflicts of interest in the review. The letter of intent is to be sent to the program staff listed under INQUIRIES.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants. Applications kits are available at most institutional offices of sponsored research or may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, Email: grantsinfo@nih.gov. Application kits are also available at: http://grants.nih.gov/grants/forms.htm

Special Instructions for Preparation of the Application

The responsibilities of the Data Management and Coordinating Center of the Network are diverse. Each of the responsibilities described in the section "Scope" under the Research Objectives is relevant to the overall performance of the Network. Applications must address each responsibility and focus in areas they may have specific expertise without having to address components beyond their scope of experience or research interest.

Applicants must describe in detail the development, implementation, and maintenance plans for each responsibility. These plans should include description of design, personnel requirements, infrastructure (hardware, software, other), and costs. Applicants are encouraged to describe in their application the cost-efficient use of existing technologies.

Budget:

Reasonable consultant cost will be allowed, if the consultant is contributing directly to the conduct or development of laboratory research. Clear and quantifiable justification is required.

Budget for personnel service directly involved in the activities of the Data Management and Coordinating Center should be clearly identified.

Travel: Applicants must budget for travel and per diem expenses for Steering Committee meetings. In the first year, applicants should plan for two investigators, the principal investigator and additional staff to attend a Planning Meeting and two Steering Committee meetings. In the second and subsequent years, applicants should plan for the PI and another investigator to attend two Steering Committee meetings per year.

Applicants must budget for travel and per diem expenses for participation in Network workshops and symposia. Applicants should plan that at least two investigators will attend a workshop or symposium every year in years 2-5.

Applicants must budget $30,000 (direct cost only) each year for reserving a site for the Steering Committee and Advisory Committee meetings and other related expenses. The place and dates for the meeting will be decided by the Program Director in consultation with the Steering Committee. The use of this set aside funds is restricted and must be reviewed and approved by the Steering Committee and by the NCI.

General:

Applicants must include their specific plans for responding to the "Terms and Conditions" of the RFA. Applicants should state their willingness to collaborate and share data freely with the other Network components, to participate in planning and attending workshops and symposia, to serve on the Steering Committee and be bound by its decisions, particularly those that relate to setting priorities for quality control and validation of new or existing biomarkers, and willingness to interact with each other and the NCI in an Internet environment. Applicants must describe computer, Internet, and other communication resources for this type of interaction. Applicants should also discuss the interaction with the NCI Program Director as to how they will fulfill the responsibilities of the Network to work together cooperatively.

2. Interaction with Industry (only if applicable): It is anticipated that the creation of the Network will serve as an attractive collaborator for industry, since it will provide clinical opportunities for the evaluation of new technologies. The Network will encourage collaboration with industry on a substantial cost-sharing basis. NCI funds will be used to support the underlying infrastructure and the cost of studies not having direct implications for a company's product development or marketing strategy. However, for new technologies that are part of a company's development or product plans, the individual companies will be responsible for costs in such areas as technology standardization and quality assurance as well as scale-up of laboratory techniques, in collection and formatting of specialized data required by regulatory agencies for device approvals, in the preparation of registration documents, and in supporting a portion of the accrual to studies pivotal for registration. It is anticipated that industry participating in the Network will not charge investigators or NCI for technologies/reagents that will be evaluated in collaborative studies. NCI views the partnership with industry as an important component without resorting to the subsidization of

private companies.

Since basic research and development of new biomarkers/reagents is an objective of this effort and since active involvement by the industrial laboratories is often facilitated by the existence of adequate patent coverage, it is essential that applicants provide plans to assure such coverage, as appropriate. Since multiple institutions may be involved, the situation can become complex. Each applicant, therefore, must provide a description of the approach to be used for obtaining patent coverage, and for licensing in particular where the inventions may involve investigators from more than one institution. Attention is drawn to Bayh-Dole Act (Public Law 96-517). Pursuant to Bayh-Dole, inventions made by the extramural investigators belong to their respective institutions. This may be of concern to collaborators, especially those who are the source of proprietary biomarkers/reagents. The Cancer Therapy Evaluation Program (CTEP), NCI, is addressing this concern by obtaining voluntary agreement of participating extramural parties as described below (the following language is provided to applicants to aid in their own proposal):

-- Institution agrees to promptly notify industrial collaborators, hereafter called "Collaborator" in writing of any inventions, discoveries or innovations made by the Institution's principal investigator or any other employees or agents of Institution, whether patentable or not, which are conceived and/or first actually reduced to practice in the performance of this study using Collaborator's Study Drug (hereinafter "Institution Inventions").

-- Institution agrees to grant to Collaborator: (i) a paid-up nonexclusive, nontransferable, royalty-free, world-wide license to all Institution Inventions for research purposes only; and (ii) a time-limited first option to negotiate an exclusive, world-wide royalty-bearing license for all commercial purposes, including the right to grant sub-licenses, to all Institution Inventions on terms to be negotiated in good faith by Collaborator and Institution. Collaborator shall notify Institution, in writing, of its interest in obtaining an exclusive license to any Institution Invention within six months of Collaborator's receipt of notice of such Institution Invention(s). In the event that Collaborator fails to so notify Institution, or elects not to obtain an exclusive license, then Collaborator's option shall expire with respect to that Institution Invention, and Institution will be free to dispose of its interests in such Institution Invention in accordance with Institution's policies. If Institution and Collaborator fail to reach agreement (within 90 days, or such additional period as Collaborator and Institution may agree) on the terms for an exclusive license for a particular Institution Invention, then for a period of six months thereafter Institution shall not offer to license the Institution Invention to any third party on materially better terms than those last offered to Collaborator without first offering such terms to Collaborator, in which case Collaborator shall have a period of 30 days in which to accept or reject the offer.

-- Institution agrees that notwithstanding anything herein to the contrary, any inventions, discoveries or innovations, whether patentable or not, which are not subject Inventions as defined in 35 USC 201(e)* arising out of any unauthorized use of the Collaborator's Study drug and/or any modifications to the Study Drug, shall be the property of the Collaborator (hereinafter "Collaborator Inventions"). Institution will promptly notify the Collaborator in writing of any such Collaborator Inventions and, at Collaborator's request and expense, Institution will cause to be assigned to Collaborator all right, title and interest in and to any such Collaborator Inventions and provide Collaborator with reasonable assistance to obtain patents (including causing the execution of any invention assignment or other documents).

The RFA label available in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time. In addition, the RFA title "Early

Detection Research Network: Data Management and Coordinating Center" and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Applicants should submit a typewritten, signed original of the application, including the checklist, and three signed photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional signed photocopies of the application must also be sent to:

Ms. Toby Friedberg
Division of Extramural Activities
National Cancer Institute
6130 Executive Boulevard, Room 636
Bethesda, MD 20892
Rockville, MD 20850 (for express/courier service)

Applications must be received by July 16, 1999. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such an application must follow the guidance in the PHS Form 398 application instructions for the preparation of revised applications, including an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

All applications will be judged on the basis of the scientific merit of the proposed project and the documented ability of the investigators to meet the "RESEARCH OBJECTIVES" of the RFA.

Review Method

Upon receipt applications will be reviewed for completeness by the CSR and responsiveness by the NCI. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NCI in accordance with the review criteria stated below. As part of the initial merit review, a process will be used by the initial review group in which applications receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the National Cancer Advisory Board.

Review Criteria

The evaluation will be based on the demonstrated capabilities of the prospective applicants in relation to the needs of the RFA. The merit of each application will be evaluated carefully, based on review criteria below. Applicants must submit information to permit evaluation of their applications. Failure to provide the information required to evaluate the application may result in rejection of the proposal without further consideration.

1. Understanding of Responsibilities: Does the principal investigator understand the objectives, and methods, and responsibilities for accomplishing the goals of the RFA? Has the applicant adequately addressed the responsibility as indicated in the "Scope"? Has the applicant provided evidence of understanding the relevant technical problems and their timely and effective solutions?

2. Personnel: Are the principal investigator and support personnel adequately trained and qualified for participating and managing multi-institutional collaboration? Do the proposed staff have capabilities, qualifications, and experience to perform tasks of the RFA? The key staff shall include PI and other investigators directly contributing to the logistic support and the data analysis.

3. Environment: Are facilities and equipment for data storage, data security and data analysis appropriate to support the objectives of the RFA? Has the applicant demonstrated adequacy of proposed infrastructure; unique features for collaborative research; commitment and documented evidence of institutional support for proposed endeavor, and institutional support for computer services including Internet access?

In addition to the above criteria, the reviewers will consider the proposed research plans under the "Scope" section "Theoretical and Applied Research," using the following additional criteria:

1. Significance. Does the proposed research address an important need for statistical/analytical tools development for earlier cancer detection and risk assessment. What is the immediacy of the research opportunity? Over the project period, is there potential for the applicant to develop statistical and analytical approaches other than those specified in the application?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed and appropriate to the aims of the proposed research? Does the applicant acknowledge potential problem areas and consider alternative tactics? Can these approaches be generally applicable to all biomarkers/reagents?

3. Innovation. Will the proposed Data Management and Coordinating Center employ novel concepts, approaches or methods? Does the proposed approach/methodology challenge existing paradigms or develop new computational/statistical approaches? Will the approaches advance the field of cancer detection and risk assessment? Has the applicant adequately addressed his/her institutional patent policy, if applicable?

4. Investigators. Are the principal investigator and his/her collaborators appropriately trained and well suited to carry out this work, especially in the area of statistical, mathematical and computation biology? To what extent do these investigators have the necessary complementary skills? Have collaborations been established or consultants identified to provide the appropriate depth and breadth of scientific expertise required for the project? Will this team of investigators contribute unique skills to the overall Network?

Additional Considerations:

1. Interactions. Are there adequate plans for effective interaction and coordination with the other components of the Consortium, the Steering Committee, the Data Management and Coordinating Center, and the NCI? Do the investigators state their willingness to collaborate and share information? Do the investigators state their willingness to abide by the priorities and policies agreed upon by the Steering Committee for Network collaborative studies?

2. Budget. For U01 applications, does the apportionment of the budget reflect that the applicants understand the requirements of managing the Data Management and Coordinating Center in the Network enterprise?

AWARD CRITERIA

The intent of this RFA is to enable the NCI to assemble the Data Management and Coordinating Center, composed of highly qualified investigators whose complementary scientific skills and expertise will enable them to achieve the goal of coordinating the activities of the Network successfully. The NCI will choose the applicant who will collectively provide the Network the most creative approaches to coordinate and data management activities with the ultimate goal of successful development and validation of biomarkers, and the range of statistical, mathematic and computation experience to ensure that the biomarkers/reagents that are validated as appropriate for various aspects of cancer research are derived efficiently.

U01 applications recommended by the National Cancer Advisory Board will be considered for an award based upon (a) scientific and technical merit; (b) the importance of the proposed research; (c) the degree of originality and innovation in research design; (d) the creativity of the approaches; (e) the likelihood for substantial contribution by the applicants to a successful collaborative Early Detection Research Network; (f) the evidence for willingness to work cooperatively; (g) the quality and availability of scientific expertise, infrastructure and resources; (h) consideration for the geographical diversity; and (i) the availability of funds.

Schedule

Letter of Intent Receipt Date:	June 11, 1999
Application Receipt Date:	July 16, 1999
Review by NCAB Advisory Board:	February 14-16, 2000
Earliest Anticipated Start Date:	April 1, 2000

EVALUATION OF THE NETWORK (for information only)

The establishment of improved strategies for the identification of individuals with small neoplastic or preneoplastic lesions with reasonable probability of progression (and that are amenable to cure) is the primary goal of this research program. It is anticipated that the research will develop and evaluate an ensemble of biological markers that will indicate the presence of early cancer or preneoplastic events. An ensemble of markers is likely to be more useful and a better predictor of disease status than a single marker or a narrow range of markers that might focus only on one or two pathways in carcinogenesis. The development and application of an ensemble of markers will require a multidisciplinary, multi-institutional approach, such as the Network presented here.

This RFA is not the only way to support a collaborative discovery and clinical evaluation of biomarkers. Before deciding whether the Early Detection Research Network should be reissued, the NCI wishes to have an assessment of the effectiveness of this mechanism over the first few years of its operation. The evaluation process will include members of the various advisory groups of the NCI, such as the Board of Scientific Advisors and the National Cancer Advisory Board, to help assess the program against the criteria established by the Steering Committee. The NCI staff will present biennial reports to the NCI Board of Scientific Advisors.

INQUIRIES

Due to the complex application format and complexity of this RFA, the NCI encourages potential applicants to take this opportunity to clarify any issues or questions. Written and telephone inquiries concerning the RFA are welcome.

Direct inquiries regarding programmatic issues to:

Sudhir Srivastava, Ph.D., M.P.H.
Early Detection Branch, Division of Cancer Prevention
National Cancer Institute
Executive Plaza North, Room 330F
Bethesda, MD 20892
Telephone: (301) 496-3983
FAX: (301) 402-0816
Email: ss1a@nih.gov

Direct inquiries regarding review issues to:

Ms. Toby Friedberg
Division of Extramural Activities
National Cancer Institute
6130 Executive Boulevard, Room 636, MSC-7399
Bethesda, MD 20892-7399
Rockville, MD 20850 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: tf12w@nih.gov

Direct inquiries regarding fiscal matters to:

Mr. William Wells
Grants Administration Branch
National Cancer Institute
Executive Plaza South, Room 243
Bethesda, MD 20892-7150
Telephone: (301) 496-7800 ext. 250
FAX: (301) 496-8601
Email: wellsw@gab.nci.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.393 Cancer Cause and Prevention Research. Awards are made under authorization of the Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under PHS grants policies and Federal Regulations [42 CFR Parts 52 and 45 CFR Part 74 and Part 92 when applicable for State and Local governments]. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.